Genome-wide survival study identifies a novel synaptic locus and polygenic score for cognitive progression in Parkinson's disease

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Supplementary Information Inventory

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List of Acknowledgements

Harvard Biomarkers Study (including HBS and HBS2 parts). Co-Directors: Brigham and Women's Hospital: Clemens R. Scherzer, Massachusetts General Hospital: Bradley T. Hyman; Investigators and Study Coordinators: Brigham and Women's Hospital: Yuliya Kuras, Karbi Choudhury, Nada Laroussi, Daly Franco, Michael T. Hayes, Nutan Sharma, Vikram Khurana, Claudio Melo De Gusmao, Chizoba C. Umeh, Reisa Sperling; Massachusetts General Hospital: John H. Growdon, Michael A. Schwarzschild, Albert Y. Hung, Aleksandar Videnovic, Alice W. Flaherty, Deborah Blacker, Anne-Marie Wills, Steven E. Arnold, Ann L. Hunt, Nicte I. Mejia, Anand Viswanathan, Stephen N. Gomperts, Mark W. Albers, Maria Allora-Palli, David Hsu, Alexandra Kimball, Scott McGinnis, John Becker, Randy Buckner, Thomas Byrne, Maura Copeland, Bradford Dickerson, Matthew Frosch, Theresa Gomez-Isla, Steven Greenberg, Julius Hedden, Elizabeth Hedley-Whyte, Keith Johnson, Raymond Kelleher, Aaron Koenig, Maria Marquis-Sayagues, Gad Marshall, Sergi Martinez-Ramirez, Donald McLaren, Olivia Okereke, Elena Ratti, Christopher William, Koene Van Dij, Shuko Takeda, Anat Stemmer-Rachaminov, Jessica Kloppenburg, Catherine Munro, Rachel Schmid, Sarah Wigman, Sara Wlodarcsyk; Data Coordination: Brigham and Women's Hospital: Thomas Yi; Biobank Management Staff: Brigham and Women's Hospital: Idil Tuncali. We thank all study participants and their families for their invaluable contributions. HBS is made possible by generous support from the Harvard NeuroDiscovery Center, with additional contributions from the Michael J Fox Foundation, NINDS U01NS082157, U01NS100603, and the Massachusetts Alzheimer's Disease Research Center NIA P50AG005134.

DIGPD: Steering committee: Jean-Christophe Corvol (Pitié-Salpêtrière Hospital, Paris, principal investigator of DIGPD), Alexis Elbaz (CESP, Villejuif, member of the steering committee), Marie Vidailhet (Pitié-Salpêtrière Hospital, Paris, member of the steering committee), Alexis Brice (Pitié-Salpêtrière Hospital, Paris, member of the steering committee and PI for genetic analysis) ; Statistical analyses: Alexis Elbaz (CESP, Villejuif, PI for statistical analyses), Fanny Artaud (CESP, Villejuif, statistician); Principal investigators for sites (alphabetical order): Frédéric Bourdain (CH Foch, Suresnes, PI for site), Jean-Philippe Brandel (Fondation Rothschild, Paris, PI for site), Jean-Christophe Corvol (Pitié-Salpêtrière Hospital, Paris, PI for site), Pascal Derkinderen (CHU Nantes, PI for site), Franck Durif (CHU Clermont-Ferrand, PI for site), Richard Levy (CHU Saint-Antoine, Paris, PI for site), Fernando Pico (CH Versailles, PI for site), Olivier Rascol (CHU Toulouse, PI for site); Co-investigators (alphabtical order): Anne-Marie Bonnet (Pitié-Salpêtrière Hospital, Paris, site investigator), Cecilia Bonnet (Pitié-Salpêtrière Hospital, Paris, site investigator), Christine Brefel-Courbon (CHU Toulouse, site investigator), Florence Cormier-Dequaire (Pitié-Salpêtrière Hospital, Paris, site investigator), Bertrand Degos (Pitié-Salpêtrière Hospital, site investigator), Bérangère Debilly (CHU Clermont-Ferrand, site investigator), Alexis Elbaz (Pitié-Salpêtrière Hospital, Paris, site investigator), Monique Galitsky (CHU de Toulouse, site investigator), David Grabli (Pitié-Salpêtrière Hospital, Paris, site investigator), Andreas Hartmann (Pitié-Salpêtrière Hospital, Paris, site investigator), Stephan Klebe (Pitié-Salpêtrière Hospital, Paris, site investigator), Julia Kraemmer (Pitié-Salpêtrière Hospital, site investigator), Lucette Lacomblez (Pitié-Salpêtrière Hospital, Paris, site investigator), Sara Leder (Pitié-Salpêtrière Hospital, Paris, site investigator), Graziella Mangone (Pitié-Salpêtrière Hospital, Paris, site investigator), Louise-Laure Mariani (Pitié-Salpêtrière Hospital, Paris, site investigator), Ana-Raquel Marques (CHU Clermont Ferrand, site investigator), Valérie Mesnage (CHU Saint Antoine, Paris, site investigator), Julia Muellner (Pitié-Salpêtrière Hospital, Paris, site investigator), Fabienne Ory-Magne (CHU Toulouse, site investigator), Violaine Planté-Bordeneuve (Henri Mondor Hospital, Créteil, site investigator), Emmanuel Roze (Pitié-Salpêtrière Hospital, Paris, site investigator), Melissa Tir (CH Versailles, site investigator), Marie Vidailhet (Pitié-Salpêtrière Hospital, Paris, site investigator), Hana You (Pitié-Salpêtrière Hospital, Paris, site investigator); Neuropsychologists: Eve Benchetrit (Pitié-Salpêtrière Hospital, Paris, neuropsychologist), Julie Socha (Pitié-Salpêtrière Hospital, Paris, neuropsychologist), Fanny Pineau (Pitié-Salpêtrière Hospital, Paris, neuropsychologist), Tiphaine Vidal (CHU Clermont-Ferrand, neuropsychologist), Elsa Pomies (CHU de Toulouse, neuropsychologist), Virginie Bayet (CHU de Toulouse, neuropsychologist); Genetic core: Alexis Brice (Pitié-Salpêtrière Hospital, Paris, PI for genetic studies), Suzanne Lesage (INSERM, ICM, Paris, genetic analyses), Khadija Tahiri (INSERM, ICM, Paris, lab technician) Hélène Bertrand (INSERM, ICM, Paris, lab technician), Graziella Mangone (Pitié-Salpêtrière Hospital, Paris, genetic analyses); Sponsor activities and clinical research assistants: Alain Mallet (Pitié-Salpêtrière Hospital, Paris, sponsor representative), Coralie Villeret (Hôpital Saint Louis, Paris, Project manager), Merry Mazmanian (Pitié-Salpêtrière Hospital, Paris, project manager), Hakima Manseur (Pitié-Salpêtrière Hospital, Paris, clinical research assistant), Mostafa Hajji (Pitié-Salpêtrière Hospital, Paris, data manager), Benjamin Le Toullec (Pitié-Salpêtrière Hospital, Paris, clinical research assistant), Vanessa Brochard (Pitié-Salpêtrière Hospital, Paris, project manager), Monica Roy (CHU de Nantes, clinical researh assistant), Isabelle Rieu (CHU Clermont-Ferrand, clinical research assistant), Stéphane Bernard (CHU Clermont-Ferrand, clinical research assistant), Antoine Faurie-Grepon (CHU de Toulouse, clnical research assistant).

PreCEPT/PostCEPT Study: PreCEPT/PostCEPT Steering Committee: University of Rochester: David Oakes, Ira Shoulson; University of Toronto: Anthony E. Lang; Parlinson's Institute: Caroline Tanner; Institute for Neurodegenerative Disorders: Kenneth Marek; Voyager Therapeutics: Bernard Ravina; Brigham and Women's Hospital: Clemens Scherzer, University of Ottawa: Michael

Schlossmacher, Avid Radiopharmaceuticals: Andrew Siderowf, We thank the Parkinson Study Group (PSG) PreCEPT/PostCEPT investigators for the acquisition of high-quality clinical data, careful follow up of study subjects and collection of blood samples.

DATATOP: We thank the investigators of the Parkinson Study Group (PSG) DATATOP for the acquisition of high-quality clinical data, careful follow-up of study subjects, and DNA collection in the DATATOP cohort.

PICNICS: Roger Barker, Caroline Williams-Gray, David P Breen, Gemma Cummins, Jonathan Evans, Sophie Winder-Rhodes, Ruwani Wijeyekoon contributed to the trial design, and the recruitment and assessment of patients and DNA sample collection and preparation. The PICNICS study was sponsored by the University of Cambridge/Cambridge University Hospitals NHS Trust UK and received funding from the Cure Parkinson's Trust, the Van Geest Foundation, Parkinson's UK, and the NIHR Cambridge Biomedical Research Centre.

CamPaIGN: Roger Barker, Tom Foltynie, Caroline Williams-Gray, Trevor Robbins, Carol Brayne, Sarah Mason, Sophie Winder-Rhodes contributed to the design and running of the trial as well as the recruitment and assessment of patients and DNA sample collection and preparation. Ruwani Wijeyekoon contributed to DNA sample preparation. The CamPaIGN study was sponsored by the University of Cambridge UK and has received funding from the Wellcome Trust, the Medical Research Council, the Patrick Berthoud Trust, and the NIHR Cambridge Biomedical Research Centre.

PROPARK/PROPARK-C: The PROPARK study was headed by Jacobus J. van Hilten and Johan Marinus.

PDBP: Data and biospecimens used in preparation of this manuscript were obtained from the Parkinson's Disease Biomarkers Program (PDBP) Consortium, supported by the National Institute of Neurological Disorders and Stroke at the National Institutes of Health. Investigators include: Roger Albin, Roy Alcalay, Alberto Ascherio, Thomas Beach, Sarah Berman, Bradley Boeve, F. DuBois Bowman, Shu Chen, Alice Chen-Plotkin, William Dauer, Ted Dawson, Paula Desplats, Richard Dewey, Ray Dorsey, Jori Fleisher, Kirk Frey, Douglas Galasko, James Galvin, Dwight German, Lawrence Honig, Xuemei Huang, David Irwin, Kejal Kantarci, Anumantha Kanthasamy, Daniel Kaufer, James Leverenz, Carol Lippa, Irene Litvan, Oscar Lopez, Jian Ma, Lara Mangravite, Karen Marder, Laurie Orzelius, Vladislav Petyuk, Judith Potashkin, Liana Rosenthal, Rachel Saunders-Pullman, Clemens Scherzer, Michael Schwarzschild, Tanya Simuni, Andrew Singleton, David Standaert, Debby Tsuang, David Vaillancourt, David Walt, Andrew West, Cyrus Zabetian, Jing Zhang, and Wenquan Zou. The PDBP Investigators have not participated in reviewing the data analysis or content of the manuscript.

PPMI: Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org. PPMI, a public-private partnership, is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners, including Abbvie, Allergan, Avid, Biogen Idec, BioLegend, Bristol-Myers Squibb, DENALI, GE Healthcare, Genentech, GlaxoSmithKline, Lilly, Lundbeck, Merck, Meso Scale Discovery, Pfizer, Piramal, Roche, SANOFI GENZYME, SERVIER, Takeda, TEVA, UCB and GOLUB CAPITAL.

Arizona Study of Aging/Brain and Body Donation Program: National Institute of Neurological Disorders and Stroke, U24 NS072026 National Brain and Tissue Resource for Parkinson's Disease and Related Disorders; National Institute on Aging, P30 AG19610 Arizona Alzheimer's Disease Core Center; Arizona Department of Health Services, Arizona Alzheimer's Consortium; Arizona Biomedical Research Commission, Arizona Parkinson's Disease Consortium; Michael J. Fox Foundation for Parkinson's Research.

NET-PD LS1: We would like to thank the patients and families who participate in the NET-PD LS1 study. The following additional NINDS grants supported the Net-PD LS-1 study: U01NS043127, U01NS043128, and U10NS44415-44555 from the National Institute of Neurologic Disorders and Stroke.

Tartu/Perron: We would like to thank all patients and families who participated in the study. Support by the institutional research grants IUT20–46 of the Estonian Ministry of Education and Research and by the H2020 ERA-chair grant (agreement 668989, project Transgeno) is appreciated.

ParkWest: Principal investigators: Guido Alves (Norwegian Centre for Movement Disorders, Stavanger University Hospital), Ole-Bjørn Tysnes (Haukeland University Hospital). Investigators and study coordinators: Karen Herlofson, Solgunn Ongre, Siri Bruun (Sørlandet Hospital Arendal); Ineke HogenEsch, Marianne Kjerandsen, Liv Kari Håland (Haugesund Hospital); Wenche Telstad, Aliaksei Labusau, Jane Kastet (Førde Hospital); Bernd Müller, Geir Olve Skeie, Charalampos Tzoulis (Haukeland University Hospital); Kenn Freddy Pedersen, Michaela Dreetz Gjerstad, Elin Bjelland Forsaa, Jodi Maple-Grødem, Johannes Lange, Veslemøy Hamre Frantzen, Anita Laugaland, Karen Simonsen, Ingvild Dalen (Stavanger University Hospital). The ParkWest study has

received funding from the Western Norway Regional Health Authority (grant number 911218), and the Norwegian Parkinson's Disease Association, and the Research Council of Norway (grant number 287842).

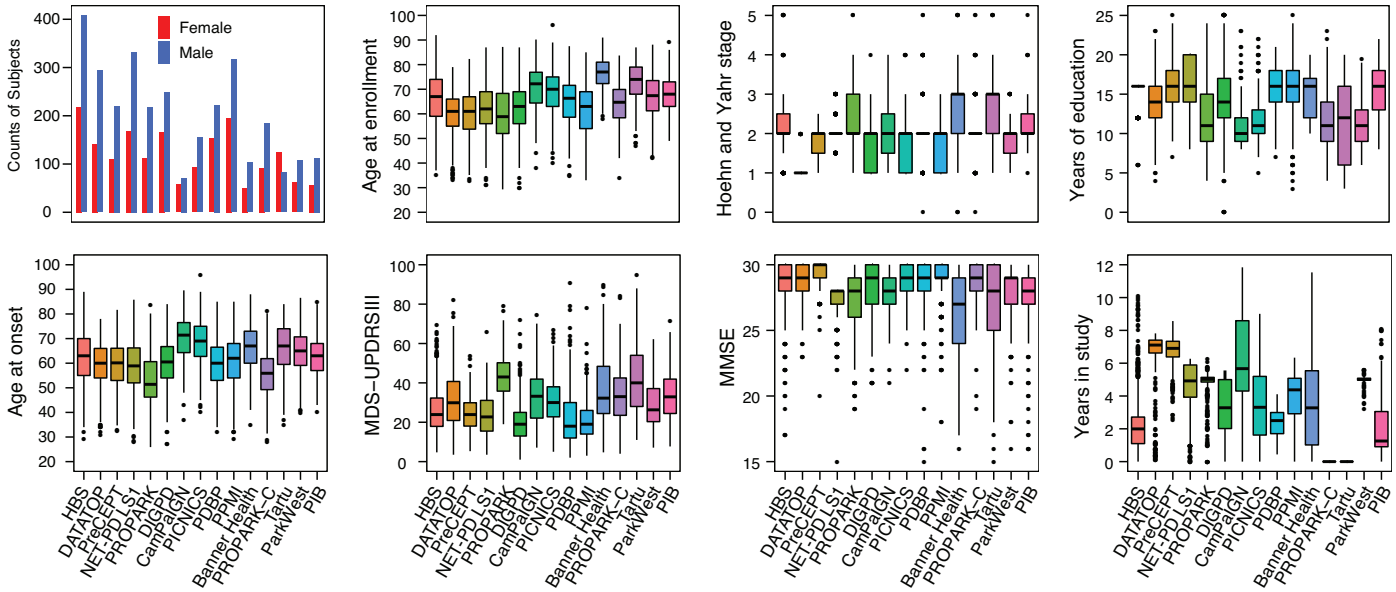
PIB funding: NIH grants: NS075321 and NS097437, the American Parkinson Disease Association (APDA), the Greater St. Louis Chapter of the APDA, the Barnes Jewish Hospital Foundation (Elliot Stein Family Fund, Parkinson disease research fund).

DeNoPa: This study was supported by unrestricted grants from the Paracelsus-Elena-Klinik, Kassel, Germany, EU Grant: Horizon 2020/propag-ageing, the Michael J Fox Foundation for Parkinson's Research, ParkinsonFonds Deutschland, and TEVA Pharma. Staff: Jens Ebentheuer, Tamara Wicke and Elisabeth Lang, Maritta Starke and Birgit Otte, Martina Schaumburg and Nicolai Cogal.

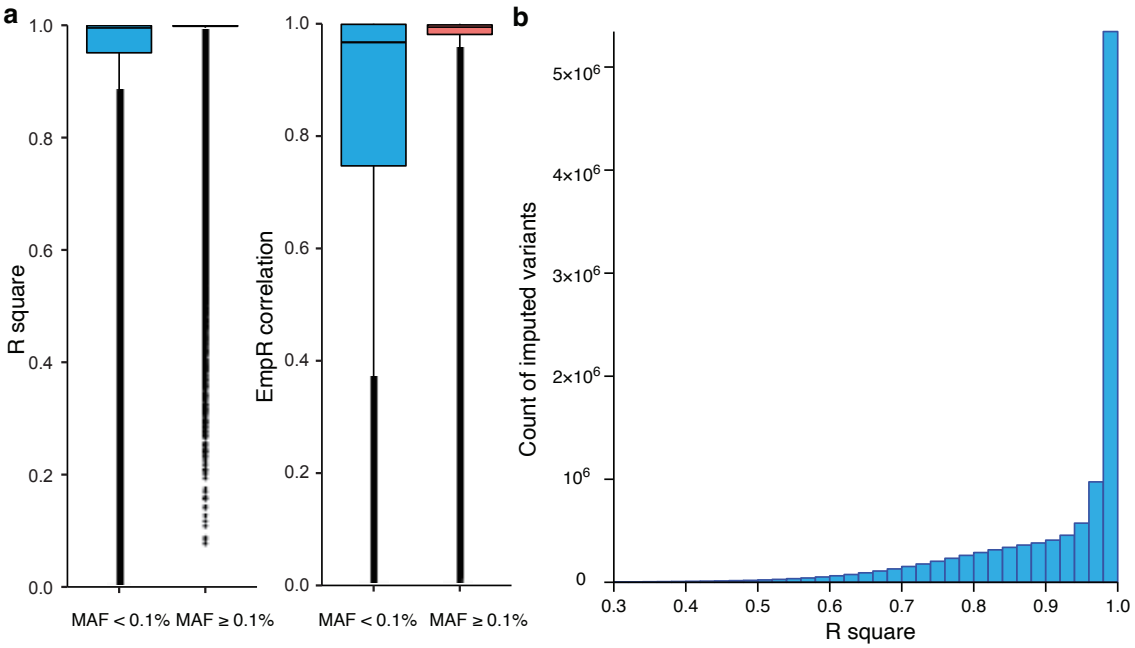
EPIPARK: We would like to acknowledge Katja Lohmann, Eva Juliane Vollstedt, Norbert Brueggemann and the EPIPARK team, Grants KA3179/2-1. Collection of the EPIPARK cohort was partially funded by the DFG (FOR 2488). We also acknowledge Annika Klee, who helped to extract the data needed for this work and parts of the clinical data used here will be part of her doctoral thesis.

The Genotype-Tissue Expression (GTEx) Project was supported by the Common Fund of the Office of the Director of the National Institutes of Health, and by NCI, NHGRI, NHLBI, NIDA, NIMH, and NINDS. The data used for the analyses described in this manuscript were obtained from: GTEx Analysis V7 release (dbGaP Accession phs000424.v7.p2) of GTEx Portal on 12/11/2017.

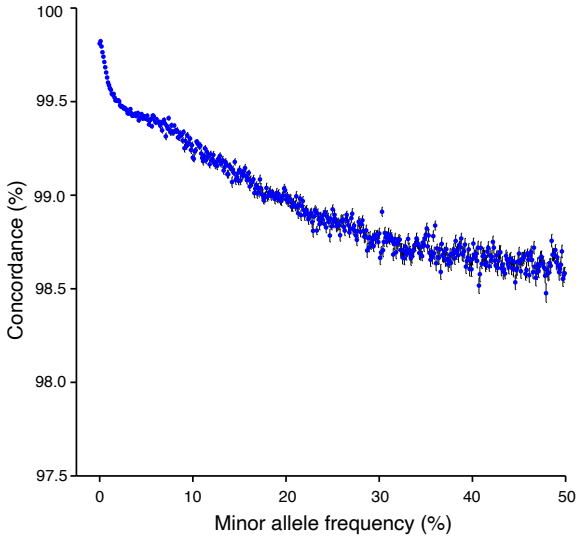
Translational Genomics Core of Partners HealthCare Personalized Medicine: We are grateful to Alison Brown for her expertise in Multi-Ethnic Genotyping Array genotyping.



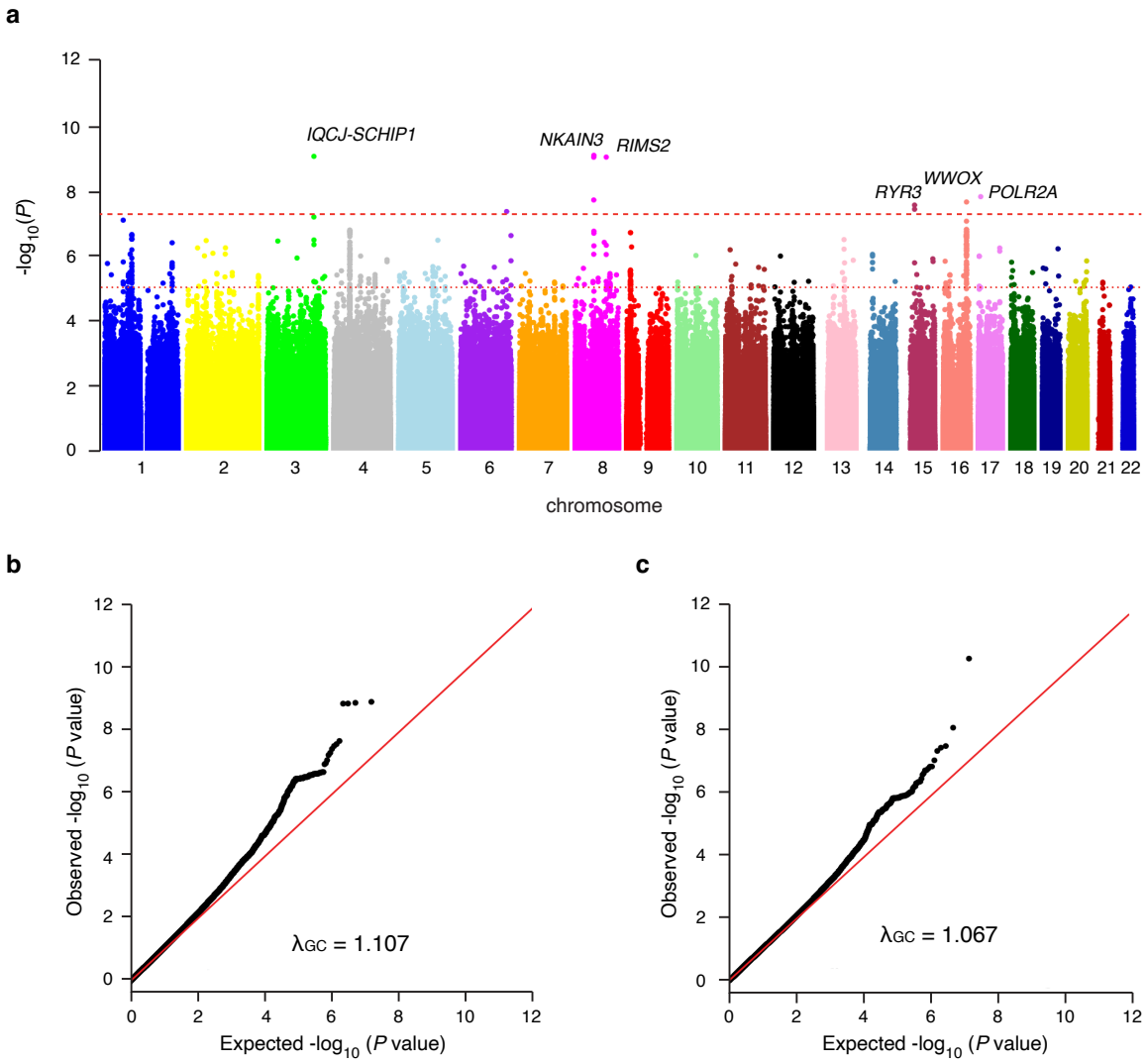
Supplementary Figure 1. Baseline characteristics of PD patients in each discovery and replication cohort. Box plots show the median and the first and third quartiles of values; the ends of the whiskers represent the lowest (or highest) value still within 1.5-times the inter-quartile range. Outliers outside this range are shown as dots. Number of PD patients represented in each cohort: HBS (n = 626); DATATOP (n = 435); PreCEPT (n = 330); NET-PDLS1 (n = 501); PROPARK (n = 330); DIGPD (n = 414); CamPIGIN (n = 129); PICNICS (n = 248); PDBP (n = 375); PPMI (n = 512); Banner Health (n = 153); PROPARK-C (n = 276); Tartu (n = 206); ParkWest (n = 169); PIB (n = 168).



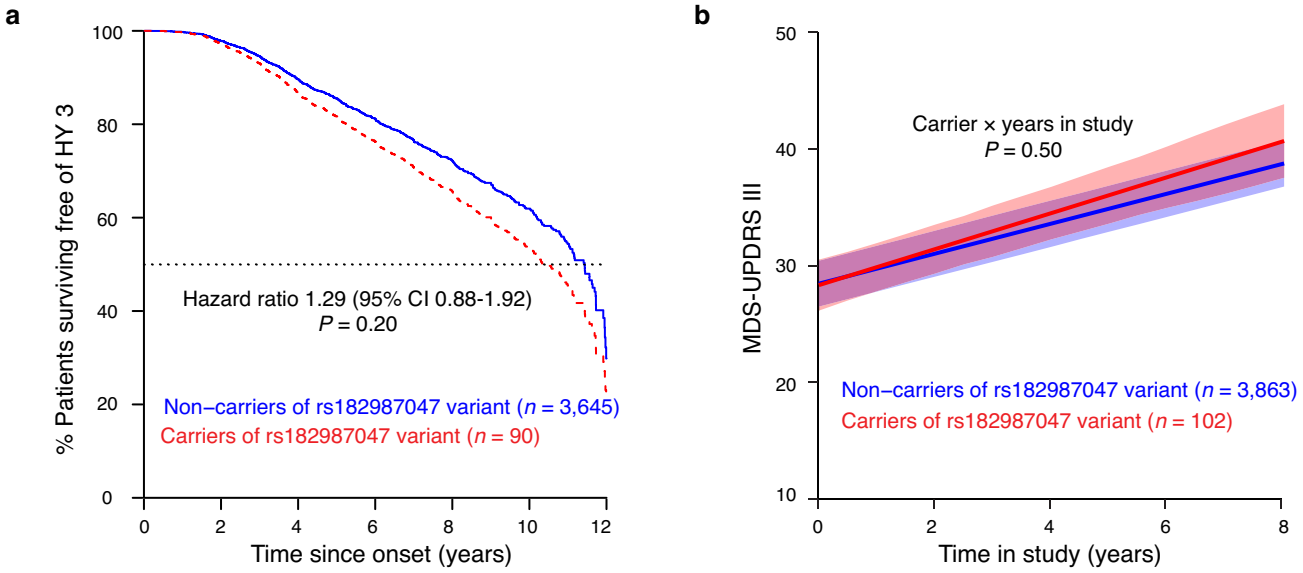
Supplementary Figure 2. Imputation quality. **a**, To estimate imputation accuracy, imputed genotype calls for 1,052,012 SNPs were compared with directly genotyped data using EmpR to calculate the correlation between the true genotyped values and the imputed values from the output of Minimac3. Mean R^2 was 0.996 and EmpR was 0.979 for variants with MAF ≥ 0.1%. Variants with MAF ≥ 0.1% (n = 824,728) showed significant higher R^2 and EmpR ($P \approx 0$ and $P \approx 0$, one sided Mann–Whitney U test) compared to variants with MAF < 0.1% (n = 227,284). Box plots show the median and the first and third quartiles of values; the ends of the whiskers represent the lowest (or highest) value still within 1.5-times the inter-quartile range. Outliers outside this range are shown as dots. **b**, Distribution of R^2 of imputed variants (n = 11,273,228) with MAF ≥ 0.1% and R^2 ≥ 0.3. MAF, minor allele frequency.



Supplementary Figure 3. High concordance between imputed genotypes derived from the MEGA chip and whole genome sequencing of 562 samples. We employed the SnpSift tool (http://snpeff.sourceforge.net/SnpSift.version_4_0.html) to evaluate the concordance between imputed SNPs (based on the MEGA array) and SNPs directly called from whole genome sequencing in 562 individuals from HBS for which both assays were available. The percent concordance between 10,421,269 imputed SNPs and whole genome sequencing was 99.4% (standard error = 0.0006%). The figure shows the percent concordance. Each dot represents the mean percent concordance of variants per minor allele frequency (in windows of 0.1% increments) in 562 HBS participants. Error bar represent the +/- s.e.m. around the mean percent concordance values.



Supplementary Figure 4. a, Manhattan plot showing results for the within-cases, longitudinal genome-wide survival study in the discovery population. -log10(*P* value) from the Cox proportional hazards model for 12-year survival free of dementia are plotted against chromosomal position for the discovery population (*n* = 2,650 patients with 11,744 visits). Each point represents a SNP. The dashed red line corresponds to the genome-wide significance threshold. Quantile-quantile plot for the analysis of discovery (**b**) and combined population (**c**). Quantile-quantile plot of the observed -log10(*P* values) versus the expectation under the null hypothesis. Data are presented for association with PD dementia in the discovery population and in the combined population after imputation and quality control (MAF ≥ 1%). The overall genomic control inflation factor ($\boldsymbol{\lambda}_{GC}$) was 1.107 in discovery and 1.067 in the combined population, respectively. The LD Score regression intercepts[1] of 1.086 in the discovery and 1.057 in the combined population were lower than the $\boldsymbol{\lambda}_{GC}$s, which is consistent with a contribution of polygenicity to the inflation.



Supplementary Figure 5. The lead *RIMS2* variant was not statistically significantly associated with longitudinal decline in motor impairment in patients with PD. a, Covariate-adjusted survival curves for PD patients without the variant (blue line) and those carrying the variant (red dash line, combined heterozygous and homozygous). *P* value from Cox PH analysis with two-sided Wald test. **b**, Adjusted mean MDS-UPDRS III scores across time predicted from the estimated fixed-effect parameters in the linear mixed model analysis are shown for PD patients. Blue color represents PD patients without variant and red color represents those carrying a variant (combined heterozygous and homozygous); the shaded ribbons indicate +/- s.e.m. across time. *P* value from LMM analysis with two-sided *t*-tests.

Supplementary Table 1. Overview of study cohorts.

Study (Country)	Phase	*N* (% male)	Age at Enrollment (mean years, SD)	Years of Education (mean years, SD)	Study Years (mean years, range)	Hoehn and Yahr stage (mean, SD)	MDS UPDRS III[*](mean, SD)	MMSE[#] (mean, SD)
HBS (USA)	Discovery	626 (65.2%)	66.2 (10.1)	15.2 (1.8)	2.4 (0-10.1)	2.1 (0.7)	25.8 (11.8)	28.4 (2.1)
NET-PD Long term Study-1 (LS1) (USA, Canada)	Discovery	501 (66.3%)	61.8 (9.7)	15.9 (3.2)	4.4 (0-6.3)	2.0 (0.4)	23.8 (10.0)	27.3 (1.2)
DIGPD (France)	Discovery	414 (59.9%)	62.2 (9.8)	14.5 (4.8)	3.3 (0-5.6)	1.8 (0.5)	20.1 (10.3)	28.2 (1.9)
PROPARK (Netherlands)	Discovery	330 (66.1%)	59.6 (10.7)	12.1 (4.2)	4.6 (0-6.3)	2.6 (0.8)	42.8 (10.9)	27.1 (2.5)
CamPaIGN (UK)	Discovery	129 (55%)	70.2 (9.7)	11.3 (3.2)	6.4 (0-12.8)	2.00 (0.7)	33.2 (14.2)	27.7 (1.8)
PICNICS (UK)	Discovery	248 (62.5%)	68.73 (9.2)	12.2 (3.1)	3.4 (0-9.0)	1.8 (0.7)	30.7 (11.7)	28.6 (1.4)
PDBP (USA)	Discovery	375 (59.2%)	65.1 (9.3)	15.9 (2.6)	2.3 (0-4.1)	2.0 (0.7)	21.1 (12.0)	28.4 (2.1)
BannerHealth (USA)	Discovery	153 (67.3%)	76.4 (7.2)	15.2 (2.7)	4.1 (0-19.9)	2.7 (1.1)	37.0 (19.7)	25.6 (4.9)
ParkWest (Norway)	Discovery	169 (63.3%)	67.1 (9.2)	11.2 (3.2)	5.0 (0-5.6)	1.8 (0.6)	28.6 (11.7)	27.9 (2.4)
PIB (USA)	Discovery	168 (66.7%)	67.6 (8.2)	15.7 (2.7)	2.1 (0-8.1)	2.4 (0.5)	33.6 (12.3)	27.3 (3.1)
PROPARK-C[&] (Netherlands)	Discovery	276 (66.7%)	64.0 (8.4)	11.8 (3.7)	0	2.1 (0.7)	34.4 (15.3)	28.5 (1.7)
DATATOP (USA, Canada)	Replication	435 (67.6%)	60.0 (9.0)	14.3 (3.4)	6.3 (0-7.8)	1.0 (0.1)	31.9 (13.8)	29.0 (1.4)
PreCEPT (USA, Canada)	Replication	330 (66.7%)	60.5 (9.4)	16.1 (3.2)	6.7 (0-8.6)	1.8 (0.5)	24.6 (9.2)	29.3 (1.1)
PPMI (USA)	Replication	512 (61.9%)	61.4 (10.0)	15.3 (3.4)	4.0 (0-6.3)	1.6 (0.5)	20.3 (9.4)	29.0 (1.6)
Tartu (Estonia)[&]	Replication	206 (39.8%)	72.6 (8.4)	11.00 (5.1)	0	2.8 (0.9)	42.2 (17.9)	27.0 (3.2)
DeNoPa (Germany)	Validation	159 (66.0%)	65.3 (9.7)	13.3 (2.9)	5.2 (0-7.0)	1.8 (0.7)	23.3 (12.2)	28.3 (1.6)
EPIPARK (Germany)	Validation	220 (62.3%)	64.8 (10.0)	13.8 (3.1)	2.1 (0-7.8)	2.2 (0.9)	28.3 (12.1)	27.8 (2.4)
HBS2 (USA)	Validation	141 (72.3%)	66.6 (8.1)	15.4 (1.6)	0.4 (0-1.75)	2.2 (0.6)	24.4 (11.0)	27.9 (2.4)

The studies included are the Harvard Biomarkers Study (HBS)[2,3]; Neuroprotection Exploratory Trials in PD- Long term Study-1 (NET-PD LS1)[4]; Drug Interaction with Genes in PD (DIGPD)[5]; PROfiling PARKinson's disease (PROPARK) study[6]; Cambridgeshire Parkinson's Incidence from GP to Neurologist (CamPaIGN)[7-9]; Parkinsonism: Incidence, Cognition and Non-motor heterogeneity in Cambridgeshire (PICNICS)[10]; Parkinson's Disease Biomarkers Program (PDBP)[11]; Banner Health study(Arizona Study of Aging/Brain and Body Donation Program)[12]; ParkWest[13] and PIB[14]; Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP)[15]; Parkinson Research Examination of CEP-1347 Trial/A Longitudinal Follow-up of the PRECEPT Study Cohort (PreCEPT/PostCEPT)[16]; Parkinson's Progression Markers Initiative (PPMI)[17], De Novo Parkinson Cohort (DeNoPa)[18] EPIPARK[19], HBS2 and Tartu[20]. [*]UPDRS subscale II, III scores from HBS, DATATOP, PreCEPT, EPIPARK, HBS2 and CamPaIGN were converted into MDS-UPDRS II, III scores according to the conversion formula developed by Goetz et al.[21]. [#]The SPES/SCOPA-motor scale was converted into MDS-UPDRS III score according to Ref.[22]. The MoCA from PDBP and EPIPARK was converted into MMSE score according to Ref.[23]. SCOPA-COG were collected in PROPARK, PROPARK-C (PROPARK-Cross sectional cohort) and NET-PD LS1 cohort and converted to MMSE scores. [&]Baseline visit only.

Supplementary Table 2. Definition of Parkinson's disease dementia across study cohorts.

Study (Country)	Definition of PD dementia (PDD)
HBS (USA)	Dementia was defined using operationalized level 1 MDS dementia criteria[24]. These criteria required *1*, an MMSE < 26; *2*, cognitive deficits severe enough to impact daily living (UPDRS sub-score I item 1, Intellectual impairment score ≥ 2 indicating 'Dementia has impact on active daily living scale'); *3*, impairment in at least two cognitive domains operationalized as impairment in two of the following four tasks: ≤ 3 of 5 points in the MMSE Seven backward test (attention); abnormal clock drawing test (executive dysfunction); subscore = 0 in the MMSE Pentagons (visuo-constructive ability); and ≤ 2 of 3 points in the 3-Word Recall of the MMSE (memory performance). A Geriatric Depression Scale-15 (GDS-15) score <10 was used to indicate the absence of severe depression.
NET-PD Long-term Study-1 (LS1) (USA)	Diagnosis of dementia was based on a SCOPA-COG cut-off value of 22/23. In Ref[25], using the MDS criteria for dementia as the gold standard, maximum accuracy was attained with this cut-off value.
DIGPD (France)	Dementia was defined using the diagnostic criteria and checklist recommended for the diagnosis of PDD by the Movement Disorder task force as in Ref[26] as well as interview-based assessments with the patient and caregiver.
PROPARK (Netherlands)	Diagnosis of dementia was based on a SCOPA-COG cut-off value of 22/23. In Ref[25], using the MDS criteria for dementia as the gold standard, maximum accuracy was attained with this cut-off value.
CamPaIGN (UK)	Dementia was diagnosed on the basis of a MMSE of less than or equal to 24 and fulfillment of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for dementia as previously reported in Ref[7].
PICNICS (UK)	Dementia was diagnosed using level 1 MDS dementia criteria[24], which were operationalized in this cohort using the Addenbrooke's Cognitive Examination-Revised, tests of semantic and phonemic fluency, and the pentagon copying test as well as interview-based assessments with the patient and caregiver.
PDBP (USA)	Dementia was defined using operationalized level 1 MDS dementia criteria[24]. These criteria required *1*, a Montreal Cognitive Assessment (MoCA) score < 21[27]; *2*, cognitive deficits severe enough to impact daily living (MDS-UPDRS sub-score I item 1, Cognitive impairment score ≥ 2 as criteria for 'Dementia has impact on active daily living scale'); *3*, impairment in at least two cognitive domains operationalized as impairment in two of the following four tasks: ≤ 2 of 3 points in the MoCA seven backwards test (attention); 0 points in the MoCA language fluency test item (language); ≤ 4 of 5 points in the word recall of the MoCA (delayed recall); ≤ 4 of 5 on the MoCA visuospatial/executive test. A Hamilton Depression Rating Scale (HDRS-17) < 24[28] was used as indicating the absence of severe depression.
BannerHealth (USA)	The postmortem Clinical Dementia Rating Scale contains a set of questions from which a global summary rating, expressed on a scale of 0 to 3, is obtained. In general, subjects with a score of 0 are cognitively within normal limits for age, subjects with a score of 0.5 have cognitive impairment that does not meet criteria for dementia, subjects with a score of 1 have mild dementia, subjects with a score of 2 have moderate dementia and subjects with a score of 3 have severe dementia. On this dataset, this decision is made based on the last clinical assessment prior to death, if the last standardized assessment occurred less than 18 months prior to death. If the last assessment was done more than 18 months prior to death, then the decision is based on the postmortem diagnostic interview and/or on review of more recent private medical record.
ParkWest (Norway)	Dementia was defined using operationalized level 1 MDS dementia criteria[24].
PIB (USA)	The Clinical Dementia Rating scale (CDR)[29] was used to quantify the presence and severity of dementia. CDR 0 indicates no dementia, CDR 0.5 indicates cognitive decline (not meeting criteria for dementia), and CDR 1, 2, and 3 indicate mild, moderate, and severe dementia, respectively.
PROPARK-C (Netherlands)	Diagnosis of dementia was based on a SCOPA-COG cut-off value of 22/23. In Ref[25], using the MDS criteria for dementia as the gold standard, maximum accuracy was attained with this cut-off value.
DATATOP (USA, Canada)	For DATATOP published criteria for disabling cognitive impairment were used (cognitive impairment leading to functional impairment) as in Ref.[30].
PreCEPT (USA, Canada)	PreCEPT defined PDD as a score of 4 on the MDS-UPDRS subscale 1 item 1 defined as "cognitive dysfunction [that] precludes the patient's ability to carry out normal activities and social interactions"
PPMI (USA)	Dementia was extracted from PPMI database Cognitive_Categorization table, where Cognitive State score (COGSTATE) =3; Cognitive decline marked as 'Yes'; Any 2 or more of the following cognitive tests are >1.5 SD below the standardized mean: 1,HVLT Total Recall ≤ 35; 2,HVLT Recognition Discrimination ≤ 35; 3,Benton Judgment of Line Orientation ≤ 6; 4,Letter Number Sequencing ≤ 6; 5,Semantic Fluency Test ≤35; 6,Symbol Digit Modalities ≤ 35; Functional impairment marked as 'Yes'.

DeNoPa (Germany)	Dementia was defined using operationalized level 1 MDS dementia criteria[24]. These criteria required *1*, an MMSE < 26; *2*, cognitive deficits severe enough to impact daily living (MDS-UPDRS sub-score I item 1, Cognitive impairment score ≥ 2 indicating 'Dementia has impact on active daily living scale'); *3*, impairment in at least two cognitive domains operationalized as impairment in two of the following four tasks: ≤ 3 of 5 points in the MMSE Seven backward test (attention); abnormal clock drawing test (executive dysfunction); subscore = 0 in the MMSE Pentagons (visuo-constructive ability); and ≤ 2 of 3 points in the 3-Word Recall of the MMSE (memory performance). A Geriatric Depression Scale-15 (GDS-15) score <10 was used to indicate the absence of severe depression.
EPIPARK (Germany)	Dementia was defined using operationalized level 1 MDS dementia criteria[24]. These criteria required *1*, a Montreal Cognitive Assessment (MoCA) score < 21[27]; *2*, cognitive deficits severe enough to impact daily living (UPDRS sub-score I item 1, Intellectual impairment score ≥ 2 indicating 'Dementia has impact on active daily living scale'); *3*, impairment in at least two cognitive domains operationalized as impairment in two of the following four tasks: ≤ 2 of 3 points in the MoCA serial seven subtraction test; 0 points in the MoCA language fluency test item (language); ≤ 4 of 5 points in the word recall of the MoCA (delayed recall); ≤ 4 of 5 on the MoCA visuospatial/executive test. A Beck Depression Inventory (BDI) score ≤30 was used to indicate the absence of severe depression.
HBS2 (USA)	Dementia was defined using operationalized level 1 MDS dementia criteria[24]. These criteria required *1*, an MMSE < 26; *2*, cognitive deficits severe enough to impact daily living (UPDRS sub-score I item 1, Intellectual impairment score ≥ 2 indicating 'Dementia has impact on active daily living scale'); *3*, impairment in at least two cognitive domains operationalized as impairment in two of the following four tasks: ≤ 3 of 5 points in the MMSE Seven backward test (attention); abnormal clock drawing test (executive dysfunction); subscore = 0 in the MMSE Pentagons (visuo-constructive ability); and ≤ 2 of 3 points in the 3-Word Recall of the MMSE (memory performance). A Geriatric Depression Scale-15 (GDS-15) score <10 was used to indicate the absence of severe depression
Tartu (Estonia)	NA

NA data not available

Supplementary Table 3. Variants reaching genome-wide significance in the discovery cohort for association with risk of progression from PD to PDD.

Chr.	Position (Mb)	SNP	Risk allele	RAF	HR	95%CI of HR	*P* discovery	*P* replication	*P* combined	Nearest gene
8	63.20	rs151059677	A	0.086	2.45	1.84-3.28	1.03×10^{-9}	0.48	6.16×10^{-8}	*NKAIN3*
3	158.92	rs150468541	G	0.014	5.76	3.28-10.13	1.10×10^{-9}	0.49	3.03×10^{-8}	*IQCJ*
8	105.25	rs182987047	T	0.013	4.74	2.87-7.83	1.16×10^{-9}	0.004	2.78×10^{-11}	*RIMS2*
8	62.73	rs118029233	G	0.038	3.30	2.24-4.84	1.17×10^{-9}	0.30	2.74×10^{-6}	*RP11-705O24.1*
17	7.40	rs117248307	T	0.017	4.33	2.60-7.21	1.87×10^{-8}	0.80	6.80×10^{-7}	*POLR2A*
8	62.81	rs118004610	C	0.039	2.87	1.98-4.15	2.37×10^{-8}	0.92	1.67×10^{-6}	*RP11-705O24.1*
16	78.52	rs142789964	T	0.014	3.49	2.25-5.42	2.72×10^{-8}	0.59	1.95×10^{-6}	*WWOX*
15	33.83	rs148485629	A	0.022	4.04	2.46-6.62	3.38×10^{-8}	0.66	1.43×10^{-6}	*RYR3*
15	33.83	rs142839796	C	0.022	4.01	2.44-6.59	4.53×10^{-8}	0.66	1.74×10^{-6}	*RYR3*

Variants reaching genome-wide significance ($P < 5 \times 10^{-8}$) in the discovery population for association with risk of progression from PD to PDD. Hazard ratio for developing PDD in patients with PD carrying a risk allele. Chr., chromosome; RAF, risk allele frequency; HR, hazard ratio from discovery population; 95% CI, 95% confidence interval for the hazard ratio. Chromosome and physical position according to hg19. *P* values from Cox PH analysis with two-sided Wald test.

Supplementary Table 4. Analysis of candidate variants for cognitive decline in PD.

Genetic factor	HR	95%CI of HR	Nominal *P*	Subjects (*N*)
GBA mutations[9,31,32]	1.93	1.36-2.73	0.0002	Carriers (371); Non-carriers (3,450)
APOE ε4 allele[33-37]	1.48	1.17-1.87	0.001	*APOE* ε4/ε4 (73); ε4/ε3, ε4/ε2 (912); Others (2,836)
LRRK2 Gly2019Ser[38,39]	0.27	0.04-1.99	0.2	Heterozygous carriers (95); Non-carriers (3,726)
SNCA rs356219 G/A[33]	0.92	0.77-1.10	0.34	Homozygous carriers (732); Heterozygous carriers (1,855); Non-Carriers (1,217)
SNCA (rs62306323-C rs7689942-T Haplotype)[40]	0.78	0.52-1.17	0.22	Carriers (501); Non-carriers (3,320)
MAPT H1 vs. H2[33,35,41-43]	1.30	1.02-1.67	0.036	H1/H1 (2,548); H1/H2 (1,132); H2/H2 (141)
COMT Val158Met[36,44]	0.99	0.84-1.18	0.92	Homozygous carriers (983); Heterozygous carriers (1,912); Non-Carriers (926)
BDNF Val66Met[45-47]	0.91	0.73-1.14	0.41	Homozygous carriers (148); Heterozygous carriers (1,172); Non-Carriers (2,501)

The Cox PH statistic was used to estimate the influence of each genetic factor on time (years from PD onset) to reaching the endpoint of PD dementia in the combined dataset (n = 3,821). Age at onset of PD, gender and years of education, as well as ten principal components were included as covariates in the Cox PH model and a "cohort" term was included as a random effect. HR, hazard ratio. Nominal *P* values are shown; for the evaluation of these 8 candidate genes previously associated with cognitive decline in PD the multiple-testing adjusted significance threshold was defined as 0.00625 (e.g. 0.05/8). *P* values from Cox PH analysis with two-sided Wald test.

Supplementary Table 5. Association of lead GWAS-derived susceptibility variants with progression to PDD.

PD susceptibility SNP	CHR:BP	Risk Allele	RAF	OR	95% CI of OR	GWAS nominal *P*	Nearest gene	HR	95% CI of HR	Cox *P*[#]	Bonferroni-corrected *P*[##]	FDR	Power (%)
rs114138760	1:154898185	C	0.011	1.32	1.26-1.39	4.19×10^{-09}	*PMVK*	2.35	1.37-4.03	0.002	0.174	0.174	1.9
rs35749011	1:155135036	A	0.017	1.83	1.77-1.90	1.72×10^{-70}	*KRTCAP2*	1.73	1.10-2.72	0.018	1	0.333	4.4
rs76763715	1:155205634	C	0.005	2.11	1.95-2.28	1.59×10^{-22}	*GBAP1*	0.99	0.31-3.22	0.991	1	0.991	1.4
rs6658353	1:161469054	C	0.501	1.07	1.06-1.08	6.10×10^{-12}	*FCGR2A*	0.91	0.76-1.08	0.264	1	0.720	92.5
rs11578699	1:171719769	C	0.805	1.07	1.06-1.09	4.47×10^{-09}	*VAMP4*	0.96	0.76-1.20	0.699	1	0.937	56.1
rs823118	1:205723572	T	0.566	1.11	1.10-1.12	1.11×10^{-29}	*NUCKS1*	0.85	0.72-1.01	0.070	1	0.571	90.8
rs11557080	1:205737739	A	0.139	1.14	1.13-1.16	2.50×10^{-22}	*RAB29*	0.81	0.62-1.05	0.108	1	0.688	59.2
rs4653767	1:226916078	T	0.720	1.09	1.08-1.10	1.38×10^{-15}	*ITPKB*	0.87	0.72-1.07	0.186	1	0.688	77.2
rs10797576	1:232664611	T	0.140	1.12	1.10-1.13	6.84×10^{-17}	*SIPA1L2*	0.94	0.73-1.22	0.645	1	0.937	57.7
rs76116224	2:18147848	A	0.904	1.12	1.10-1.14	1.27×10^{-08}	*KCNS3*	0.97	0.72-1.31	0.855	1	0.939	17.3
rs2042477	2:96000943	T	0.758	1.07	1.06-1.08	1.38×10^{-08}	*KCNIP3*	0.91	0.75-1.11	0.339	1	0.780	69.1
rs11683001	2:102396963	A	0.337	1.07	1.06-1.08	8.04×10^{-13}	*MAP4K4*	1.01	0.83-1.22	0.938	1	0.956	91.1
rs57891859	2:135464616	A	0.719	1.08	1.07-1.10	4.55×10^{-14}	*TMEM163*	0.95	0.78-1.15	0.589	1	0.933	79.5
rs1474055	2:169110394	T	0.131	1.20	1.18-1.21	2.54×10^{-39}	*STK39*	1.07	0.84-1.37	0.562	1	0.927	58.8
rs73038319	3:18361759	C	0.041	1.18	1.16-1.21	5.94×10^{-13}	*SATB1*	1.17	0.81-1.69	0.412	1	0.825	12.9
rs6808178	3:28705690	T	0.379	1.07	1.06-1.08	8.09×10^{-12}	*LINC00693*	0.98	0.82-1.18	0.855	1	0.939	92.2
rs12497850	3:48748989	T	0.648	1.07	1.06-1.08	1.36×10^{-10}	*IP6K2*	1.07	0.89-1.28	0.493	1	0.927	86.9
rs55961674	3:122196892	T	0.172	1.09	1.08-1.10	9.98×10^{-12}	*KPNA1*	0.93	0.73-1.18	0.524	1	0.927	69.5
rs11707416	3:151108965	T	0.633	1.06	1.05-1.08	1.13×10^{-10}	*MED12L*	0.92	0.77-1.10	0.373	1	0.819	87.7
rs1450522	3:161077630	G	0.326	1.06	1.05-1.07	5.01×10^{-10}	*SPTSSB*	0.97	0.81-1.16	0.728	1	0.937	89.8
rs10513789	3:182760073	T	0.811	1.16	1.15-1.17	1.22×10^{-34}	*MCCC1*	0.93	0.74-1.16	0.518	1	0.927	54.6
rs873786	4:925376	C	0.901	1.19	1.17-1.21	1.79×10^{-21}	*GAK*	0.83	0.62-1.11	0.216	1	0.691	19.3
rs34311866	4:951947	C	0.194	1.24	1.22-1.25	9.98×10^{-70}	*TMEM175*	1.30	1.06-1.59	0.012	1	0.320	79.3
rs4698412	4:15737348	A	0.553	1.11	1.10-1.12	2.06×10^{-28}	*BST1*	0.95	0.80-1.14	0.591	1	0.933	91.1
rs34025766	4:17968811	T	0.841	1.09	1.07-1.10	2.87×10^{-10}	*LCORL*	0.89	0.71-1.11	0.303	1	0.778	48.1
rs6825004	4:77110365	C	0.691	1.06	1.05-1.08	1.17×10^{-09}	*SCARB2*	1.02	0.85-1.23	0.815	1	0.937	82.5
rs4101061	4:77147969	G	0.289	1.10	1.08-1.11	4.97×10^{-19}	*FAM47E*	1.03	0.85-1.23	0.783	1	0.937	87.9
rs6854006	4:77198054	C	0.637	1.10	1.08-1.11	5.82×10^{-21}	*FAM47E-STBD1*	1.12	0.93-1.35	0.233	1	0.691	86.1
rs356182	4:90626111	G	0.372	1.32	1.31-1.33	3.89×10^{-154}	*SNCA*	0.93	0.77-1.11	0.405	1	0.825	92.5

rs5019538	4:90636630	G	0.321	1.17	1.15-1.18	1.13×10^{-36}	*SNCA*	0.81	0.67-0.98	0.028	1	0.397	90.4
rs13117519	4:114369065	T	0.174	1.09	1.08-1.10	9.82×10^{-13}	*CAMK2D*	1.16	0.94-1.44	0.156	1	0.688	72.2
rs62333164	4:170583157	G	0.674	1.07	1.06-1.08	2.00×10^{-10}	*CLCN3*	1.03	0.85-1.25	0.752	1	0.937	84.6
rs1867598	5:60137959	G	0.098	1.17	1.15-1.19	2.52×10^{-23}	*ELOVL7*	1.13	0.85-1.50	0.404	1	0.825	42.9
rs26431	5:102365794	C	0.703	1.06	1.05-1.08	1.57×10^{-09}	*PAM*	1.16	0.95-1.41	0.135	1	0.688	80.5
rs11950533	5:134199105	C	0.898	1.10	1.08-1.11	7.16×10^{-09}	*C5orf24*	1.01	0.73-1.39	0.945	1	0.956	19.0
rs4140646	6:27738801	A	0.208	1.09	1.07-1.10	5.62×10^{-12}	*LOC100131289*	0.95	0.75-1.20	0.680	1	0.937	80.9
rs9261484	6:30108683	C	0.755	1.07	1.05-1.08	1.62×10^{-08}	*TRIM40*	1.03	0.84-1.26	0.795	1	0.937	70.4
rs112485576	6:32578772	C	0.837	1.18	1.16-1.20	6.96×10^{-28}	*HLA-DRB5*	1.05	0.82-1.36	0.687	1	0.937	39.1
rs12528068	6:72487762	T	0.284	1.07	1.06-1.08	1.63×10^{-10}	*RIMS1*	0.97	0.81-1.18	0.788	1	0.937	87.3
rs997368	6:112243291	A	0.805	1.07	1.06-1.09	1.84×10^{-09}	*FYN*	0.87	0.70-1.07	0.189	1	0.688	57.6
rs75859381	6:133210361	C	0.033	1.25	1.21-1.29	1.04×10^{-10}	*RPS12*	1.06	0.62-1.79	0.840	1	0.939	7.2
rs199351	7:23300049	A	0.594	1.11	1.10-1.12	5.25×10^{-26}	*GPNMB*	0.98	0.82-1.17	0.795	1	0.937	89.8
rs76949143	7:66009851	T	0.949	1.15	1.13-1.18	1.43×10^{-08}	*GS1-124K5.11*	1.14	0.73-1.79	0.567	1	0.927	4.8
rs1293298	8:11712443	A	0.744	1.10	1.09-1.11	3.99×10^{-16}	*CTSB*	1.12	0.89-1.42	0.325	1	0.780	74.2
rs620513	8:16697593	G	0.732	1.09	1.08-1.10	2.72×10^{-15}	*FGF20*	0.99	0.81-1.21	0.918	1	0.956	74.9
rs2280104	8:22525980	T	0.360	1.06	1.05-1.07	1.16×10^{-08}	*BIN3*	1.14	0.95-1.37	0.164	1	0.688	91.6
rs2086641	8:130901909	C	0.278	1.06	1.05-1.07	1.81×10^{-08}	*FAM49B*	1.03	0.85-1.25	0.752	1	0.937	87.4
rs13294100	9:17579690	G	0.658	1.09	1.08-1.10	8.72×10^{-18}	*SH3GL2*	1.13	0.94-1.37	0.196	1	0.688	85.7
rs10756907	9:17727065	G	0.233	1.10	1.09-1.11	5.06×10^{-17}	*SH3GL2*	0.95	0.78-1.16	0.621	1	0.937	82.2
rs6476434	9:34046391	C	0.266	1.06	1.05-1.07	6.58×10^{-09}	*UBAP2*	1.10	0.91-1.32	0.347	1	0.780	86.8
rs896435	10:15557406	T	0.689	1.08	1.07-1.09	3.41×10^{-13}	*ITGA8*	1.01	0.84-1.22	0.880	1	0.955	82.8
rs10748818	10:104015279	G	0.149	1.08	1.07-1.10	1.05×10^{-09}	*GBF1*	1.01	0.79-1.30	0.918	1	0.956	58.9
rs72840788	10:121415685	A	0.216	1.08	1.07-1.09	1.57×10^{-11}	*BAG3*	1.15	0.94-1.40	0.171	1	0.688	80.2
rs117896735	10:121536327	A	0.017	1.55	1.49-1.61	2.36×10^{-28}	*INPP5F*	0.56	0.26-1.20	0.136	1	0.688	4.7
rs7938782	11:10558777	A	0.878	1.09	1.08-1.11	2.12×10^{-09}	*RNF141*	0.96	0.72-1.28	0.782	1	0.937	26.3
rs12283611	11:83487277	C	0.585	1.07	1.06-1.08	2.61×10^{-10}	*DLG2*	0.88	0.74-1.05	0.156	1	0.688	90.4
rs3802920	11:133787001	T	0.205	1.11	1.10-1.13	6.26×10^{-20}	*IGSF9B*	0.87	0.70-1.08	0.197	1	0.688	78.7
rs76904798	12:40614434	T	0.144	1.15	1.14-1.17	1.52×10^{-28}	*LRRK2*	0.84	0.65-1.08	0.175	1	0.688	62.0
rs34637584	12:40734202	A	0.002	11.35	10.33-12.46	3.61×10^{-148}	*LRRK2*	0.27	0.04-1.99	0.199	1	0.688	1.8
rs7134559	12:46419086	C	0.596	1.06	1.05-1.07	3.96×10^{-08}	*SCAF11*	0.99	0.83-1.18	0.918	1	0.956	90.3

rs10847864	12:123326598	T	0.364	1.16	1.15-1.17	1.47×10^{-37}	*HIP1R*	1.20	1.01-1.43	0.039	1	0.397	91.8
rs11610045	12:133063768	A	0.490	1.06	1.05-1.07	1.77×10^{-10}	*FBRSL1*	1.11	0.94-1.31	0.234	1	0.691	92.7
rs9568188	13:49927732	T	0.740	1.06	1.05-1.08	1.15×10^{-08}	*CAB39L*	0.96	0.78-1.17	0.676	1	0.937	72.4
rs4771268	13:97865021	T	0.230	1.07	1.06-1.08	1.45×10^{-09}	*MBNL2*	1.04	0.85-1.28	0.680	1	0.937	80.6
rs12147950	14:37989270	C	0.562	1.05	1.04-1.06	3.54×10^{-08}	*MIPOL1*	0.79	0.66-0.94	0.009	0.812	0.320	91.1
rs11158026	14:55348869	C	0.676	1.09	1.08-1.10	1.66×10^{-16}	*GCH1*	1.12	0.93-1.35	0.245	1	0.691	83.4
rs3742785	14:75373034	A	0.787	1.07	1.06-1.09	1.92×10^{-09}	*RPS6KL1*	0.85	0.69-1.05	0.128	1	0.688	64.0
rs979812	14:88464264	T	0.442	1.06	1.05-1.07	6.19×10^{-11}	*GALC*	0.92	0.77-1.09	0.335	1	0.780	92.8
rs2251086	15:61997385	C	0.858	1.13	1.11-1.14	6.08×10^{-18}	*VPS13C*	0.95	0.73-1.23	0.703	1	0.937	31.5
rs6497339	16:19277493	A	0.454	1.07	1.05-1.08	2.76×10^{-11}	*SYT17*	1.03	0.86-1.22	0.765	1	0.937	92.8
rs2904880	16:28944396	G	0.691	1.07	1.06-1.08	7.87×10^{-10}	*CD19*	1.07	0.88-1.29	0.507	1	0.927	81.7
rs11150601	16:30977799	A	0.644	1.09	1.08-1.11	5.12×10^{-20}	*SETD1A*	0.96	0.80-1.16	0.693	1	0.937	86.6
rs6500328	16:50736656	A	0.599	1.06	1.05-1.07	1.82×10^{-09}	*NOD2*	0.92	0.77-1.09	0.332	1	0.780	90.0
rs3104783	16:52636242	A	0.434	1.07	1.06-1.08	1.29×10^{-12}	*CASC16*	0.86	0.71-1.02	0.090	1	0.674	92.7
rs10221156	16:52969426	G	0.907	1.12	1.10-1.14	1.08×10^{-10}	*CHD9*	1.40	1.02-1.93	0.040	1	0.397	19.5
rs12600861	17:7355621	C	0.352	1.06	1.05-1.07	1.01×10^{-08}	*CHRNB1*	0.91	0.76-1.09	0.292	1	0.774	91.0
rs12951632	17:40741013	T	0.735	1.07	1.06-1.08	1.40×10^{-09}	*RETREG3*	1.13	0.93-1.39	0.221	1	0.691	72.9
rs2269906	17:42294337	A	0.653	1.07	1.05-1.08	6.24×10^{-10}	*UBTF*	0.93	0.78-1.11	0.413	1	0.825	85.1
rs850738	17:42434630	G	0.394	1.07	1.06-1.08	1.29×10^{-11}	*FAM171A2*	1.20	1.02-1.42	0.031	1	0.397	92.4
rs62053943	17:43744203	C	0.845	1.31	1.29-1.33	3.58×10^{-68}	*CRHR1*	1.33	1.00-1.75	0.049	1	0.439	35.1
rs117615688	17:43798308	G	0.933	1.26	1.23-1.30	6.71×10^{-16}	*CRHR1*	1.18	0.76-1.83	0.461	1	0.902	6.4
rs11658976	17:44866805	G	0.420	1.06	1.05-1.08	3.52×10^{-08}	*WNT3*	0.98	0.81-1.17	0.803	1	0.937	92.5
rs61169879	17:59917366	T	0.164	1.09	1.07-1.10	9.28×10^{-10}	*BRIP1*	0.96	0.76-1.20	0.696	1	0.937	67.4
rs666463	17:76425480	A	0.833	1.08	1.07-1.09	3.20×10^{-09}	*DNAH17*	1.15	0.91-1.45	0.246	1	0.691	50.1
rs1941685	18:31304318	T	0.498	1.05	1.04-1.06	1.69×10^{-08}	*ASXL3*	0.99	0.83-1.18	0.934	1	0.956	92.6
rs12456492	18:40673380	G	0.318	1.10	1.09-1.11	3.80×10^{-23}	*RIT2*	0.98	0.82-1.17	0.822	1	0.937	90.8
rs8087969	18:48683589	G	0.450	1.06	1.05-1.07	1.41×10^{-08}	*MEX3C*	1.05	0.89-1.25	0.559	1	0.927	92.8
rs55818311	19:2341047	C	0.306	1.07	1.06-1.08	4.18×10^{-10}	*SPPL2B*	0.79	0.65-0.95	0.014	1	0.320	89.4
rs77351827	20:6006041	T	0.128	1.08	1.07-1.10	8.87×10^{-09}	*CRLS1*	0.92	0.70-1.21	0.558	1	0.927	53.3
rs2248244	21:38852361	A	0.283	1.07	1.06-1.09	2.74×10^{-11}	*DYRK1A*	1.06	0.88-1.27	0.565	1	0.927	87.4

Notably, 90 lead GWAS variants associated with PD susceptibility were selected from a recent meta-analysis study[48]. The threshold for statistical significance in this analysis considering multiple testing was defined as a nominal $P < 0.0005555556$ (e.g. 0.05/90 tests). CHR., chromosome; BP, hg19 position. OR, odds-ratio; RAF,

Risk allele frequency (PD susceptibility); HR, hazard ratio; FDR, False Discovery Rate. [#]Nominal *P* values from the Cox PH analysis with two-sided Wald test, adjusting for age at onset of PD, gender, years of education, ten principal components, and a "cohort" term included as a random effect. [##]The Bonferroni-corrected *P* values were adjusted for 90 tests. Power was calculated to detect an effect equivalent to HR = 1.25, sample size = 3,821, event rate = 0.255, alpha = 0.000555556 using exact variance formula from survSNP package[49] in R.

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